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THE COMPUTERIZED ANALYSIS OF ECHOCARDIOGRAMS IN THE CLINICAL EVALUATION OF ETOMIDATE

LLOYD NEAL FRIEDMAN

1979

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THE COMPUTERIZED ANALYSIS OF
ECHOCARDIOGRAMS
IN THE CLINICAL EVALUATION OF
ETOMIDATE

A Thesis Submitted to the Yale University School
of Medicine in Partial Fulfillment of the Requirement
for the degree of Doctor of Medicine

Lloyd Neal Friedman 1979

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Introduction:

In this study, the ease and flexibility with which computers can interface with medical technology is explored. Specifically, a procedure is described where echocardiograms are analyzed and, in combination with additional patient data, yield information pertinent to ventricular function. The focus of the study is a new intravenous hypnotic, etomidate. Its effect on left ventricular function will be compared to that of thiopental.

The computer by no means replaces the reader whose expertise remains an integral part of echocardiographic interpretation. It merely assists to make the analysis as simple and as rapid as possible.

There have been recent advances in the automatic analysis of echocardiograms.[1,4] The advantage lies in the consistency of the method of analysis. However, the computer, once programmed, is inflexible. It cannot make adjustments for unexpected errors unless it has been specifically programmed to do so.

Due to its non-invasive properties, ultrasound is a valuable tool for assessing the functional status of the heart. The alternative methods include cardiac catheterization and isotope imaging,[2,3] both of which are invasive procedures. Nuclear imaging is currently used in the calculation of ejection fractions and

cardiac outputs and,although less invasive than catheterization, it still involves an injection of a radioactive material and requires suitable precautions.

The frequency with which a non-invasive procedure can be used to take repeated measurements makes it ideal for interfacing with a computerized system. The large volume of data that is generated makes a computer necessary for both analysis and storage.

The major task of this study will be discussed in the section on methods.

The Etomidate Study will be a test case for the computerized system.

Background:

The Use of Echocardiograms in Determining Left Ventricular Functions:

Notwithstanding the desirability of echocardiograms, we must establish the reliability of quantifying left ventricular functions by this method. Ultrasound signals are rapidly attenuated by air filled structures. Therefore, due to surrounding lung, the "window" of ultrasound access to the heart is very small. Information obtained from the M-mode echoes is a one-dimensional signal that varies with time. Only one diameter of the left ventricular cavity can be obtained and must be extrapolated to a three-dimensional volume. This process requires a number of assumptions, but it has been studied over the past few years and has been proven feasible.

A more precise method for studying left ventricular dimensions is the real-time scanner which images a two-dimensional plane through the long axis of the left ventricle. This two-dimensional view of the ventricle allows for the approximation of the third dimension.

To determine accurate volumes from M-mode echoes a regression formula is employed to correct for the geometrical assumptions made for the shape of the left ventricle. The regression equation can be calculated by comparing ultrasound readings with left ventricular

volumes obtained from thermodilution (or dye dilution) cardiac outputs or from angiographic results.

A major clinical problem is the determination of volumes in the diseased heart. Since most patients requiring left ventricular function studies have diseased hearts, it is important to determine how variations such a wall motion abnormalities interfere with echo results. Valvular regurgitation also presents a specific problem. Stroke volumes may be accurate, but echo prediction of cardiac output will be erroneously high due to regurgitation of a portion of the ejected blood. It has also become apparent that heart rate and systemic arterial pressure must be considered in the evaluation of cardiac functions by echocardiogram[5]

Several studies have shown good correlation of ultrasound and angiographic calculations of left ventricular volumes. Fortuin et al[6] measured left ventricular dimensions and volumes in 27 patients with various cardiac abnormalities. He compared ultrasound measurements with those obtained by biplane angiography and found good correlation. Pombo et al[7] had excellent correlation between ultrasound and angiography in 27 patients. Feigenbaum et al[8] also found significant correlation between ultrasound measurements and angiography measurements at end-systole and end-diastole in 42 patients. Belenkie

et al[9] studied 40 patients with cardiac disease and used 18 patients with technically excellent results. He stated that there was good correlation between angiography and ultrasound.

A fault of these preceding studies is that the ultrasound and angiographic measurements were not made simultaneously. Linhart et al[10] described some of the defects in the studies performed to assess the reliability of echocardiography. He states that four assumptions must be true before translating the minor axis into a three-dimensional volume: " (1) that the longitudinal cross-sectional geometry is known and is the same in all persons (present thinking assumes it to be an ellipse); (2) that its three-dimensional shape is this two-dimensional figure rotated on its minor axis; (3) that these two conditions are true in both systole and diastole, in volume overloaded and in pressure overloaded states, in ischemic heart disease and in primary myocardial disease; and (4) that the major axis of the left ventricle is constant or is a constant known multiple of the minor axis in all patients in systole and in diastole." He then states that none of these assumptions is true, and points out that in each of the studies comparing ultrasound and angiography a different regression equation was employed. If the

results were combined, the correlation would not be reliable.

Linhart's critique is too severe. The geometric limitations are overcome by employing a regression equation. Each previous study, examined individually, is a valid study. Linhart does state that one-dimensional echoes are appropriate in following the clinical course of a single patient. This is important in the Etomidate Study because individual patients are studied at repeated intervals during the induction of anesthesia. Valuable information is derived from the trends observed in each patient.

Teichholz et al[11] retrospectively studied 100 left ventriculograms in the RAO projection and derived a regression formula for volumes using the minor axis. They then studied 24 patients, 12 with asynergy and 12 controls, using angiography and echocardiography. The variability in his results suggest possible problems in the use of M-mode echocardiography for the calculation of ventricular volumes in patients with coronary artery disease and possible left ventricular asynergy.

In a later study, Teichholz et al[15] showed that B-scan ultrasonography (gated two-dimensional imaging) can overcome the limitations associated with asynergy. When compared with angiography, ejection fractions had a

correlation of r=.92 in normal patients and r=.87 in patients with left ventricular asynergy.

Ludbrook et al[12] also studied one-dimensional wall motion abnormalities and found that although volume calculations may be in error, the mean velocity of circumferential fiber shortening remains a reliable index of left ventricular performance.

Acute alterations in heart rate and systemic arterial pressure are known to influence echocardiographic measurements of left ventricular performance. Hirshleifer et al[5] showed the impact of this effect on the normalized mean velocity of circumferential fiber shortening, but there have been no studies to delineate the effects of ventricular dimension measurements.

An excellent study by Popp and Harrison[13] compares echocardiographic stroke volumes in 30 patients with volume readings obtained simultaneously at catheterization using the Fick principle. This experiment acquired simultaneous data and is thus quite reliable. The correlation coefficient found between the two studies was r=.966. In the same paper the severity of valvular regurgitation was estimated by comparing the forward stroke volume determined by the Fick method with the total left ventricular stroke volume determined by the echocardiographic method. This is a useful comparison.

It can be done routinely during cardiac catheterizations.

Fortuin ét al[14] showed the reproducibility of echocardiographic measurements in evaluating a wide variety of ambulatory patients. He studied five groups: (1) normal: (2) mitral stenosis; (3) compensated volume overload; (4) idiopathic hypertrophic subaortic stenosis; and (5) congestive heart failure. Although no angiographic correlations were made, reliable patterns in volume measurements in each of the five categories were determined.

Although there are limitations in the use of ultrasound for volume calculations, it appears that they can be overcome if they are understood. If only technically good ultrasound examinations are analyzed in cases where the anatomical landmarks are well defined, and allowance is made for abnormalities that interfere with interpretations, the volumes derived from the minor axis will be cliically reliable.

Digitizers:

Interfacing a computer with a digitizer permits fast and accurate analysis of graphic information. This type of input device has proven useful in areas of medicine that require quantification of linear distance in diagnostic tests. Using this graphic input, total lung capacities can be calculated from PA and lateral x-rays and electrocardiograms can be analyzed. The area under the curves of serum electrophoresis spikes can be quantified. Graphic information such as the monthly temperature chart can also be stored.

There are many ways of inputting graphic information and many devices developed for this purpose. A terminal with a cathode ray tube makes use of "cursor lines" to establish the coordinates of a point. The position of both lines is set by hand and is a clumsy process. Another device is a "light-pen" which responds to light from a television tube, and electronically records the coordinates, but the instrument is relatively inaccurate. The common drawback of these methods is that they employ cathode ray tube displays and cannot analyze information on paper.

The "tablet" and the "sonic digitizer" are two instruments that are capable of dealing with paper printouts in a rapid and efficient manner. Both are

accurate to one one-hundredth of an inch. The "tablet" uses magnetic fields and is very useful in two dimensions. The "sonic digitizer" is just as useful and has both advantages and limitations. A spark is emitted upon depression of the pen point and the sound is received by two microphones at right angles to one another, representing x and y axes. Since the spark is several millimeters away from the penpoint, the pen must always be held with the same orientation to ensure consistency. Spatial coordinates are established by the speed with which the sound of the spark reaches each microphone. Therefore anything which obstructs the path, e.g. extraneous paper or a hand, will impede the signal and increase the reported distance. Nevertheless, the device is convenient because the microphones can be mounted on any surface, including the face of a cathode ray tube.

Materials and Methods:

Materials:

The input device to be used is the Science Accessories Corporation's NT-501 digitizer, also known as the "grafpen". It is an ultrasonic digitizer with an accuracy of one one-hundredth of an inch at the proper temperature and humidity. The pen can be set to input points into a computer individually,or continuously as a line is being drawn. The machine can be adjusted to acquire point coordinates at the rate of one every five seconds or as fast as 60 pulses per second, depending on the information capacity of the terminal. A built-in microprocessor is able to calculate the area inside a closed curve. This is useful in reading real-time echocardiograms.

The data obtained is printed out on a teletype and transmitted over a phone link to a computer. The computer used in this study is an IBM 371-58 with a four megabyte capacity. A time sharing system is employed, and many operators can use the computer simultaneously. The computer divides its time equally among users, continuously cycling its attention to each operator for a very brief period of time. For this reason each data point must be verified, and a Deckwriter II terminal is used to send the initial instructions necessary to run the computer program.

The programming language is Fortran IV.

Communication between the computer and the input/output devices is done by a telephone link using an Andersen-Jacobson interface which converts acoustic messages sent by the computer into electrical signals, and converts electrical signals created at the input device into acoustic signals that can be transmitted across phone lines. Therefore, this program does not require a private computer. The computerized analysis is accessible to any person with an input device and a phone.

The source of the data analyzed is the standard ultrasound M-mode printout. This represents a one-dimensional view of the heart and its internal structures as they vary in position with time. Distances between structures can be accurately gauged by comparing them with one-half second time markers and one centimeter distance markers. In addition an electrocardiogram is displayed so that the contractile state of the heart can be assessed.

Methods,

Introduction:

To use the digitizer efficiently, a work board is designed to set aside separate areas for control commands and the actual input of data.

The area for control commands is called a "menu" and consists of the parameters, e.g. left ventricular end-diastolic dimension, that are necessary for the study. The purpose of the menu is to simplify the analysis procedure. One merely designates a parameter on the menu instead of typing it in at the terminal. Thus one need never leave the digitizer while the program is running.

The total surface area is fourteen inches by fourteen inches, or 196 square inches. Thirty square inches, or three by ten inches is set aside for the menu. Each function control resides in a box measuring one square inch and is bounded by a set of line segments (see p.23). When a function on the menu is selected the computer knows that the point is within the borders of the menu and will determine which function has been selected. The operator may then proceed to input the data related to that function. When he has entered a sufficient number of trials, he need only select another function listed in the menu. The computer then prints out the results of its analysis and readies itself for the input of data

related to the function just selected. This process continues until the entire echocardiogram has been analyzed.

Numerical information such as the patient's blood pressure must also be entered in this study. To type it in directly would defeat the purpose of the digitizer. The ideal solution lies in utilizing the space already provided by the menu in much the same way as one uses upper and lower case on a typewriter. Ten of the menu boxes are assigned the numbers zero through nine. Another box is set aside for the function "BP". When this function is selected, a subprogram is called up that reads the systolic and diastolic blood pressures from the menu as if they were being entered directly from a typewriter. After this task has been completed, the subprogram relinquishes control to the main program, and the menu functions are interpreted as before. This process can be extended to include other types of numerical input.

The interactive aspects of the system are useful in eliminating sources of error and in ensuring that the operator follows procedures correctly. "Interactive" refers to the ability of the operator and the computer to communicate with one another while the program is running. The computer, by printing instructions on the

teletype, asks the operator to do the proper standardizations before entering data. It also prints out each set of coordinates to verify that it has received the information. This is an important consideration in a time sharing system where the computer is not totally committed to your program. The operator must wait until the computer has received the data before entering the next set of data. If programmed correctly, the computer can tell the operator whether he has made an error, for example, entering a data point where he is supposed to be entering a function from the menu.

When an analysis is completed the computer prints the results. One can obtain a printout, with an impression if desired, that can be entered directly into the patient's records. This saves immeasureable time over hand calculations which must be organized and typed. Here, when the data has been entered, the analysis is complete in its final form.

The format of the printout names the function and its value and lists how many samples were averaged to arrive at this value. For calculated functions, values are printed out in sentences. An impression of the patient's cardiovascular status can then be typed at the bottom of the page.

Functions Defined:

The following functions are found on the menu:

1. RVAWD: right ventricular anterior wall thickness in diastole
2. RVAWS: right ventricular anterior wall thickness in systole
3. RVDD: right ventricular cavity dimension in diastole
4. SEPD: septal thickness in diastole
5. SEPS: septal thickness in systole
6. LVESD: left ventricular cavity dimension at end-systole
7. LVEDD: left ventricular cavity dimension at end-diastole
8. LVPWD: left ventricular posterior wall thickness in diastole
9. LVPWS: left ventricular posterior wall thickness in systole
10. LAS: maximum left atrial cavity dimension
11. AOS: aortic diameter measured at the same time as LAS
12. PA: pulmonary artery diameter at end-systole
13. MVDE: mitral valve D to E slope
14. TVDE: tricuspid valve D to E slope
15. LENGTH: length calibration
16. HAFSEC: distance of paper travel in one half second
17. LVPEP: left ventricular pre-ejection period measured from onset of Q-wave to opening of aortic valve
18. LVET: left ventricular ejection time; i.e. the time

that the aortic valve stays open

19. RVPEP: right ventricular pre-ejection period measured from the onset of the Q-wave to the opening of the pulmonic valve

20. RVET: right ventricular ejection time measured from the opening to the closing of the pulmonic valve

21. HR: heart rate; done by entering several R-R intervals

22. MVEF: mitral valve E to F slope

23. TVEF: tricuspid valve E to F slope

24. AREA: trace area of two-dimensional left ventricular section from the real time output

25. LONGAX: determine the longest axis of the two-dimensional image

26. END: ends the input, and the program proceeds to do its calculations and final printout

27. BP: initiates the blood pressure subprogram

28. BSA: initiates the body surface area subprogram

The computer calculates several values related to the information it has just received above. They are:

LVEDV: left ventricular end-diastolic volume using the Meyer formula ($LVEDV=-19.12+14.58 \times LVEDD + .62(LVEDD)^3$)

LVESV: left ventricular end-systolic volume using the Meyer formula

EF: ejection fraction (LVEDV-LVESV)/LVEDV

FS: fractional shortening (LVEDD-LVESD)/LVEDD

VCF: velocity of mean circumferential fiber shortening;

FS/LVET

LVPEPET: LVPEP/LVET

RVPEPET: RVPEP/RVET

LVPEPC(Weissler): LVPEP + 0.6 x HR

RVPEPC(Weissler): RVPEP + 0.5 x HR

LVETC(Weissler): LVET + 1.6 x HR

RVETC(Weissler): RVET + 1.5 x HR

LAAO: LAS/AOS

SPLPWD: SEPD/LVPWD

WSDS: LVPWS/LVESD

LVCAVP: estimated left ventricular cavity pressure:

WSDS x 225

SYSGRAD: estimated systolic gradient: LVCAVP-BP

SV: stroke volume: LVEDV-LVESV

CO: cardiac output: SV x HR

CI: cardiac index: CO / BSA

mean BP: BP(diastole)+1/3 x (BP(systole)-BP(diastole))

Ventricular Volume (from real time):

$$(8 \times AREA^2)/(3 \times \pi \times LONGAX)$$

Procedure for Data Input:

The Etomidate Study is a study limited to left ventricular function and deals primarily with cardiac indices. The functions that are included are LVEDD, LVESD, HR, BSA, LVEDV, LVESV, SV, CO, CI, and mean BP.

To begin the analysis the M-mode paper printout is laid flat across the work board parallel to the x-axis. The menu is at the top of the workboard.

The operator then calls the computer on the telephone, places the receiver in the carrier box, logs on to the computer and runs the program. The computer asks the operator to initialize the workboard. The operator enters the (0,0) coordinate as the point in the upper left corner of the workboard. Under program control the operator then enters the LENGTH function and inputs several pairs of data points. Each pair of points represent the calibration for one centimeter distance in the patient's heart. After each point is selected, the operator must wait briefly for the computer to repeat the coordinates to ensure that it has been entered. The operator then selects the HAFSEC function and inputs pairs of half-second marks along the x-axis.. If the paper speed is 50 mm/sec, HAFSEC will equal 25 mm. The echocardiogram has now been standardized and is ready for analysis.

The heart rate function is selected and three pairs

of R-R intervals are entered. More pairs can be entered if the rhythm is irregular. When sufficient pairs have been entered, the next function, LVEDD, is selected. At this time, the heart rate is calculated using the average R-R interval, and it is immediately printed along with the number of pairs evaluated.

LVEDD has already been selected and the computer is waiting for the data. The operator must locate the section of the echocardiogram where the acoustic beam has passed through the mitral annulus and clearly shows the borders of the left ventricular cavity in end-diastole. The ventricle is at end-diastole as it is depolarizing, so a cursor on the work board is positioned at the QRS wave parallel to the y-axis and the pair of left ventricular border points are entered for three separate beats. When the next function, LVESD is selected, the computer prints out the average LVEDD value and the number of trials averaged.

LVESD is analyzed in exactly the same way except that end-systole is chosen to be the time at which the ventricular borders are in closest approximation.

When the BP or BSA functions are selected, subprograms are run that read number values directly from the digitizer as previously described.

When the function END is selected, the computer

ceases to interact with the operator and proceeds to perform the final calculations and the formalized printout.

The entire process just described lasts approximately four minutes and results in a typewritten list of ventricular functions. If performed manually, even with a hand calculator, this process would take from fifteen minutes to half an hour.

MENU

0	1	2	3	4	5	6	7	8	9
RVAWD	RVAWS	RVDD	SEPD	SEPS	LVESD	LVEDD	LVPWD	LVPWS	LAS
AOS	PA	MVDE	TVDE	LENGTH	HAFSEC	LVPEP	LVET	RVPEP	RVET
HR	MVEF	TVEF	AREA	LONGAX	END	BP	BSA		

Cardiovascular Effects of Etomidate and Thiopental:

Thiopental is a widely used drug in the induction of anesthesia. Because of the cardiovascular changes that occur during induction, there is a search for a more benign intravenous agent. The effects of thiopental after conventional pre-anesthetic medication include:[16] (1) a decrease in cardiac output; (2) an increase in total calculated peripheral resistance; (3) no change or a fall in mean arterial blood pressure - this is thought to be caused in part by histamine release; (4) an increase or no change in heart rate; (5) a decrease in cerebral blood flow with a marked fall in cerebrospinal fluid pressure.

Etomidate is a new intravenous hypnotic agent developed in 1971 which appears to have less of a depressant effect on the cardiovascular system.

It has been compared with thiopental in dogs and is found to be superior in all categories measured.[18] There was a 60% increase in heart rate with thiopental and less than a 10% increase with etomidate. Thiopental decreased the stroke volume by 40% while etomidate had no effect. The mean arterial pressure remained stable in both etomidate and thiopental subjects, The cardiac index fluctuated with thiopental, increasing 30% in the first minute, dropping to 10% below the control by the third

minute, and then stabilizing at control values. Etomidate values remained within 10% of the control.

In a study on human volunteers it was shown that etomidate does not release histamine.[17] This may contribute to its favorable results.

Patients with stage III and IV cardiac valvular disease were studied at surgery[19] and it appears that etomidate produced only small effects on hemodynamics with less of an increase in myocardial blood flow and consumption of oxygen by the myocardium. Thus etomidate may be advantageous for induction of anesthesia in cardiovascular risk patients.

In addition to its benefits over thiopental, etomidate was also found in these studies to be superior to methohexital, propanidid, althesin, piritramid, and ketanin.

Etomidate Study:

Digitizer Accuracy:

The accuracy of the digitizer was established before analysis of the data. Much of the input data are lengths of one inch, so this was chosen as the standard measurement. Twenty trials of measurement of ruled inch marks were performed parallel to the y-axis, and twenty trials were performed paralled to the x-axis. In both cases all values were within one one-hundredth of an inch of the standardized measurement.

Protocol Information:[*]

Twenty normal patients were selected from the ranks of preoperative candidates. Half were induced with etomidate and the other half were induced with thiopental. Six of the echocardiograms were technically unreadable, due to interference from the chest wall and lungs.

Post-premedication echodimensional values serve as the control values and are compared with values obtained the prior day and values obtained one, two, and three minutes after administration of the induction agent.

In analyzing the cardiac indices and ejection fractions, it is important to follow the trends within each patient study and not just the absolute values. Because of the problem, already discussed, of using regression formulas from other studies, it will be necessary to obtain standardizations for each patient at a later date. This will consist of a simultaneous cardiac output using the Fick principle and echocardiography.

---

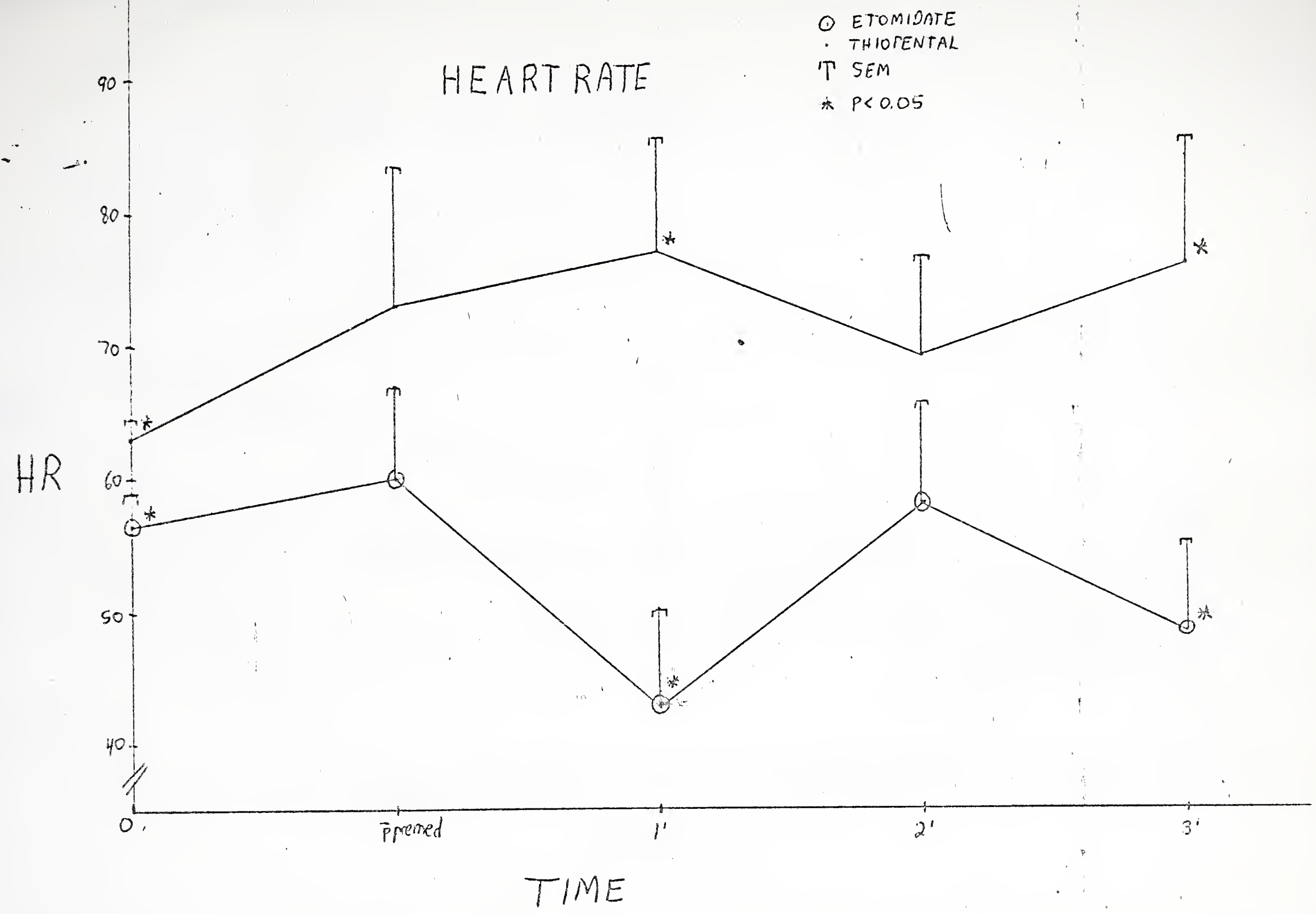
[*] see Appendix B

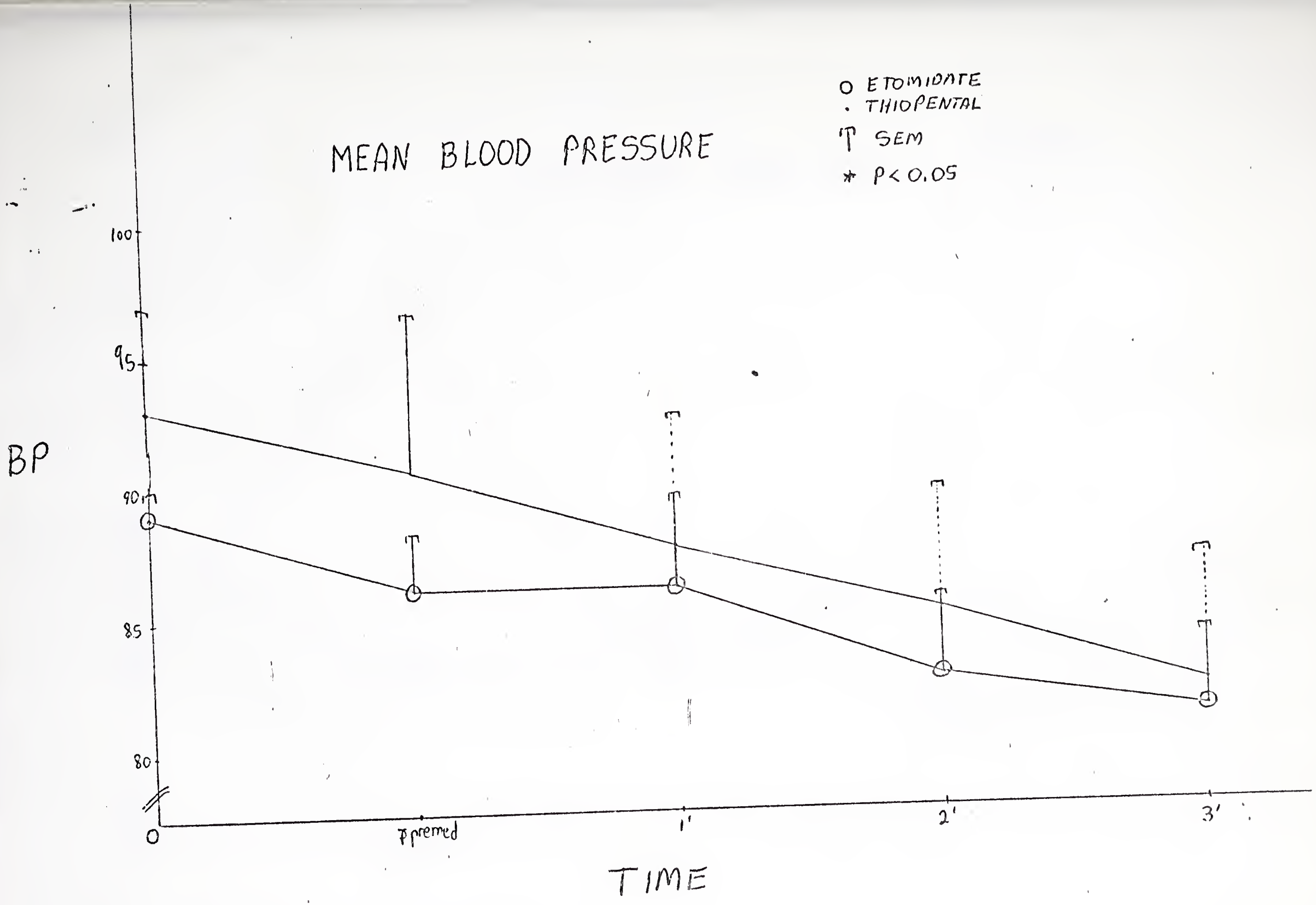
Discussion:

The results consist of an analysis of heart rate, mean blood pressure, ejection fraction, and cardiac index. Certain patterns were noted. The cardiac index and ejection fraction fluctuate unevenly with thiopental. Patients with etomidate follow a more stable pattern for all values measured. This is in agreement with the findings of previous studies. The standard error of the mean is universally smaller with the etomidate patients.

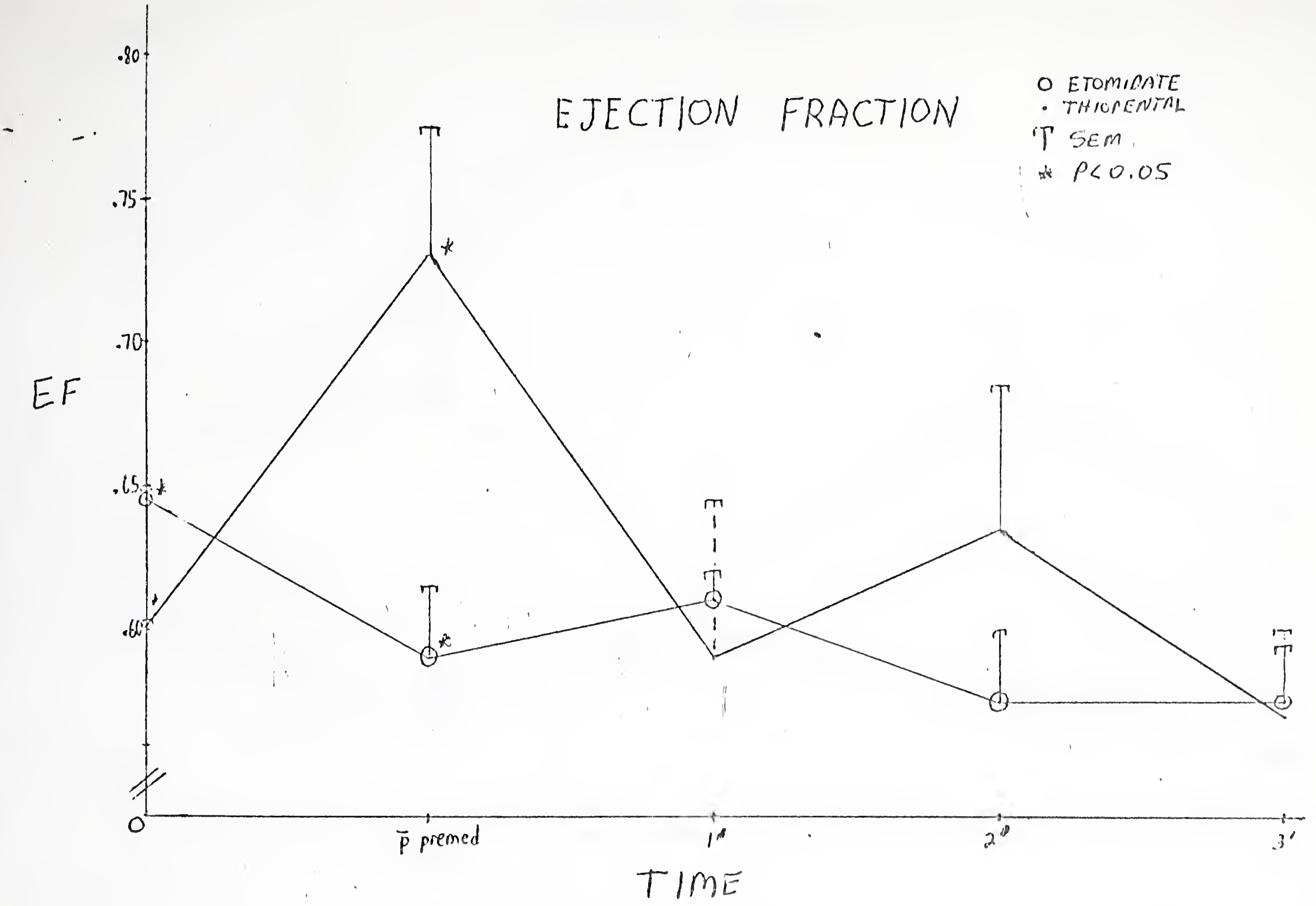
However these results are somewhat inconclusive at this time and it will be necessary to derive accurate regression formulas and reapply them to the data.

The corrected results will lend significance to the trends observed in this study.

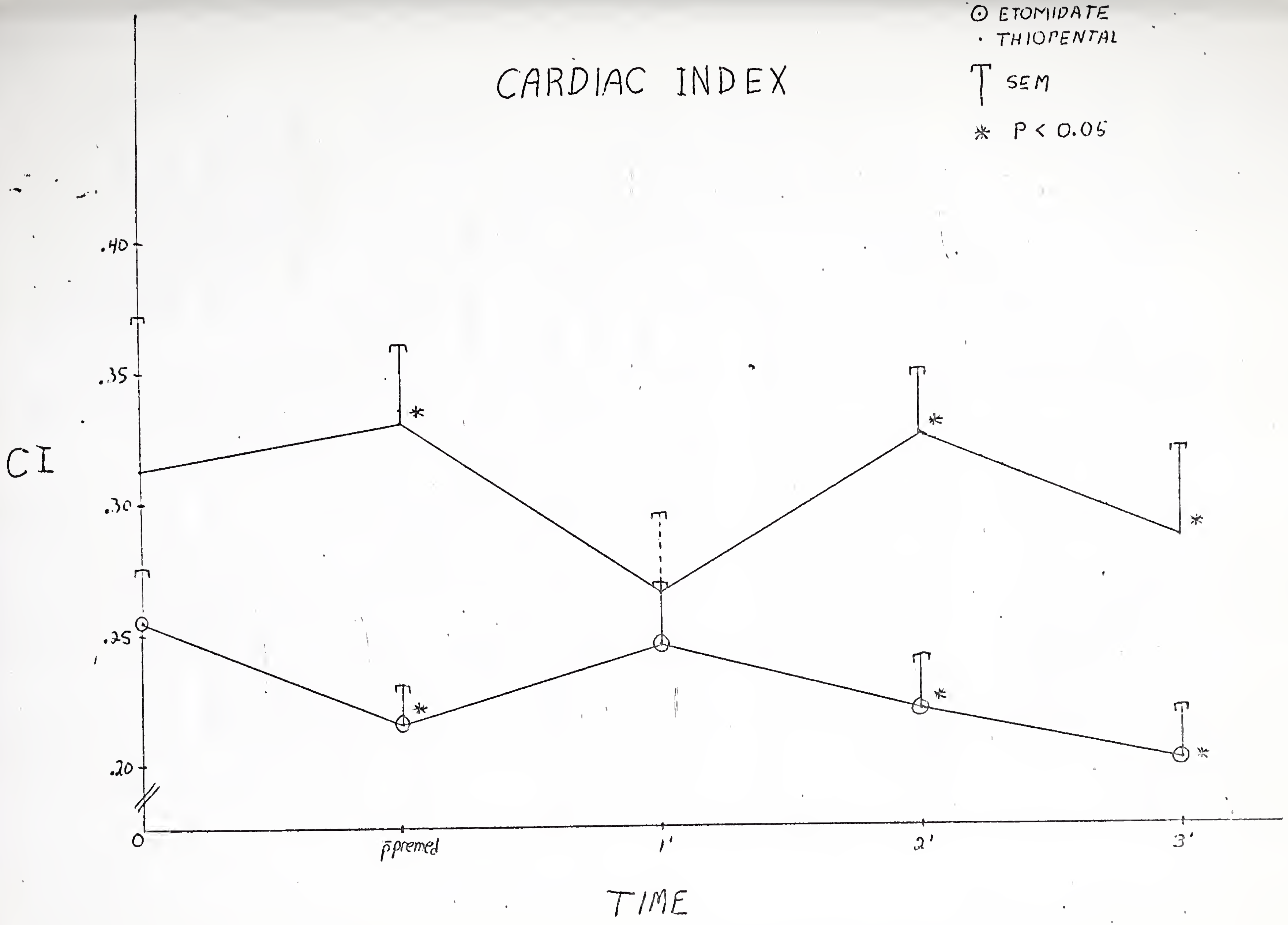

HEART RATE
ETOMIDATE
THIOPENTAL
SEM
P< 0.05
HR
90
80
70
60
50
40
TIME
0'
Premed
1'
2'
3'
*



MEAN BLOOD PRESSURE



EJECTION FRACTION


CARDIAC INDEX

Conclusion:

In summary, this program takes measurements, performs calculations and produces a printout without requiring the operator to write or type. The entire procedure takes place through the selection of coordinates with a pen on a digitizer surface.

It is the programmer's responsibility to design a program that can be implemented by a person who knows nothing about computers. There are large volumes of data which will have to be analyzed by doctors and technicians. They will rely on a method that is simple, rapid and accurate.

Although the actual measurements and calculations performed by the computer are simple, the difficulty lies in conceptualizing the best method for interacting with a computer. The algorithm in this study is designed to ask questions at the appropriate time, display error messages where needed, and make use of a menu in an efficient way. The increased complexity of the computer program makes the analysis simpler for the operator.

The ideal use of such a method is to allow several operators to utilize the same program from separate input devices. This eliminates the need for a separate microprocessor for each type of analysis. Many programs can be written for many types of analysis and can be shared by people with digitizers. In this way, operators need

purchase only input devices, e.g. isotope scanners for ejection fractions or digitizers for x-rays and ultrasound, thus minimizing equipment cost.

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Appendix A

Computer Programs

```
      INTEGER P
      REAL LENGTH,LVESD,LVEDD,LVPWD,LVPWS,LAS,MVDE,LVFEP,LVET,
     CMVEF,LVESV,LPEPET,LAAO,LVCAVP,LVEDV,LONGAX,LVPEFC,LVETC
      COMMON N,LENGTH,XSTAND,YSTAND,AVGX,AVGY,P,X,Y
C     READ IN FROM TERMINAL
      INTEGER SYSBP,DIASBP
      SYSBP=0
      DIASBP=0
      PRINT 708
  708 FORMAT (' INPUT POINTS')
C     STANDARDIZE SO HTAT THE ORIGIN IS AT (1,1)
      READ 101,X,Y
      PRINT 101,X,Y
  101 FORMAT (F6.2,F7.2)
      XSTAND=X-1.
      YSTAND=Y-1.
C     LENGTH IS THE YAXIS LENGTH CORRECTION TO 1 CM.
C     INITIALIZE IT TO 1.
      LENGTH=1.
C     READ IN THE FIRST POINT
  700 READ 101,X,Y
      PRINT 101,X,Y
C     WE SER UP A 3 X 10 INFORMATION GRID WITH AN ORIGIN AT
C     1,1 AND THE UPPER YBORDER AT 4.  UNDER THIS SYSTEM
C     ANY POINT BELOW Y=4 IS CONSIDERED A CONTROL COMMAND
C     AND NOT DATA.  THE X AND Y VALUES ARE RESET TO INTEGER
C     SO THAT ANY X,Y VALUE WITHIN A BOX OF BORDERS 1,1
C     1,2  2,1  2,2   WILL BER RESET TO 1,1. NOW STANDARDIZE
C     X.AND Y.  THE TABLET RECORDS IN INCHES SO WE WILL HAVE
C     TO CONVERT LATER TO CENTIMETERS
      X=X-XSTAND
      Y=Y-YSTAND
 9999 CONTINUE
      NEWX=X
      NEWY=Y
C     IF NEWY IS GREATER THAN 3, IT IS NOT A CONTROL COMMAND
      IF (NEWY.GT.3) PRINT 703
  703 FORMAT (' ERROR')
      IF (NEWY.GT.3) GO TO 700
C     SET UP THE GRID SO THAT EACH BOX IS ASSOCIATED WITH
C     ONE NUMBER(NEWX)
      IF(NEWY.EQ.2)NEWX=NEWX+10
      IF (NEWY.EQ.3)NEWX=NEWX+20
      IF (NEWX.EQ.26) GO TO 8888
C     WE HAVE DIVIDED OUR DATA INTO 3 SETS, THOSE WHICH NEED
C     ONLY Y VALUES, THOSE NEEDING ONLY X VALUES, AND
C       THOSE NEEDING BOTH.
C     GRIDS 1-15 NEED ONLY Y VALUES : P=1 FOR THESE
C     GRIDS 16-21 NEED ONLY X VALUES : P=2 FOR THESE
C     GRIDS 22-...  NEED BOTH : P=3 FOR THESE
```

```
00510           IF(NEWX.LE.15) GO TO 70
00520           IF(NEWX.LE.21) GO TO 71
00530 C         AT THIS POINT WE ARE LEFT WITH GRIDS 22-26
00540           IF(NEWX.EQ.24) GO TO 24
00550           IF(NEWX.EQ.27)CALL BLOOD(XSTAND,YSTAND,SYSBP,DIASBP)
00555           IF(NEWX.EQ.28) CALL BODY(XSTAND,YSTAND,BSA)
00560           P=3
00570           CALL SUM
00580 C         SUM RETURNS A LENGTH OF A LINE SEGMENT AVERAGED OVER
00590 C         SEVERAL TRIALS.  IT ALSO RETURNS THE NUMBER OF TRIALS.
00600 C        WE TAKE THIS INFO AND HANDLE IS ACCORDING T
00610 C         TO THE MANNER SPECIFIED BY THE CONTROL GRID COMMAND.
00620           IF(N.EQ.0)GO TO 9999
00630           NEWX=NEWX-21
00640           GO TO (22,23,24,25),NEWX
00650 C         WE HANDLE THE INFO FOR P=1 AND P=2 IN THE SAME FASHION.
00660  70       P=1
00670           CALL SUM
00680           IF(N.EQ.0)GO TO 9999
00690           GO TO(1,2,3,4,5,6,7,8,9,10,11,12,13,14,15),NEWX
00700  71       P=2
00710           CALL SUM
00720           IF(N.EQ.0)GO TO 9999
00730           NEWX=NEWX-15
00740           GO TO(16,17,18,19,20,21),NEWX
00750 C         NOW WE WILL PRINT OUT THE VALUES ACCORDING TO GRID
00760 C         SPECIFICATIONS
00770 C         1 IS THE CONTROL GRID VALUE FOR RVAWD
00780  1        RVAWD=AVGY
00790 C         RIGHT VENTRICULAR ANTERIOR WALL IN DIASTOLE
00800           PRINT 801,RVAWD,N
00810  801      FORMAT(' RVAWD=',F7.2,'AVERAGED OVER',I3,2X,'TRIALS')
00820           GO TO 9999
00830  2        RVAWS=AVGY
00840 C         RIGHT VENTRICULAR ANTERIOR WALL IN SYSTOLE
00850           PRINT 802,RVAWS,N
00860  802      FORMAT(' RVAWS=',F7.2,'AVERAGED OVER',I3,2X,'TRIALS')
00870           GO TO 9999
00880  3        RVDD=AVGY
00890 C         RIGHT VENTRICULAR DIASTOLIC DIMENSION
00900           PRINT 803,RVDD,N
00910  803      FORMAT(' RVDD=',F7.2,'AVERAGED OVER',I3,2X,'TRIALS')
00920           GO TO 9999
00930  4        SEPD=AVGY
00940 C         SEPTAL THICKNESS DURING DIASTOLE
00950           PRINT 804,SEPD,N
00960  804      FORMAT(' SEPD=',F7.2,'AVERAGED OVER',I3,2X,'TRIALS')
00970           GO TO 9999
00980  5        SEPS=AVGY
00990 C         SEPTAL THICKNESS DURING SYSTOLE
01000           PRINT 805,SEPS,N
```

```
01010  805  FORMAT(' SEPS=',F7.2,'AVERAGED OVER',I3,2X,'TRIALS')
01020       GO TO 9999
01030  6    LVESD=AVGY
01040 C     LEFT VENTRICULAR END SYSTOLIC DIMENSION
01050       PRINT 806,LVESD,N
01060  806  FORMAT(' LVESD=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01070       GO TO 9999
01080  7    LVEDD=AVGY
01090 C     LEFT VENTRICULAR END DIASTOLIC DIMENSION
01100       PRINT 807,LVEDD,N
01110  807  FORMAT(' LVEDD=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01120       GO TO 9999
01130  8    LVPWD=AVGY
01140 C     LEFT VENTRICULAR POSTERIOR WALL DIAMETER IN DIASTOLE
01150       PRINT 808,LVPWD,N
01160  808  FORMAT(' LVPWD=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01170       GO TO 9999
01180  9    LVPWS=AVGY
01190 C     LEFT VENTRICULAR POSTERIOR WALL DIAMETER IN SYSTOLE
01200       PRINT 809,LVPWS,N
01210  809  FORMAT(' LVPWS=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01220       GO TO 9999
01230  10   LAS=AVGY
01240 C     LEFT ATRIAL DIMENSION(MAXIMUM AT SYSTOLE)
01250       PRINT 810,LAS,N
01260  810  FORMAT(' LAS=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01270       GO TO 9999
01280  11   AOS=AVGY
01290 C     AORTA MEASURED AT SAME PERPENDICULAR AS LAS
01300       PRINT 811,AOS,N
01310  811  FORMAT(' AOS=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01320       GO TO 9999
01330  12   PA=AVGY
01340 C     PULMONARY ARTERY MEASURED MAXIMALLY AT END SYSTOLE
01350       PRINT 812,PA,N
01360  812  FORMAT(' PA=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01370       GO TO 9999
01380  13   MVDE=AVGY
01390 C     MITRAL VALVE EXCURSION FROM END SYSTOLE TO DIASTOLE(D-E
01400       PRINT 813,MVDE,N
01410  813  FORMAT(' MVDE=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01420       GO TO 9999
01430  14   TVDE=AVGY
01440 C     TRICUSPID VALVE EXCURSION(D-E)
01450       PRINT 814,TVDE,N
01460  814  FORMAT(' TVDE=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01470       GO TO 9999
01480  15   LENGTH=1./AVGY
01490 C     STANDARDIZED CORRECTION TO 1 CM
01500       PRINT 815, LENGTH
```

```
01510  815   FORMAT(' LENGTH=',F7.2)
01520        GO TO 9999
01530  16    HAFSEC=AVGX
01540 C      THIS IS THE CM EQUIVALENT OF HALF A SECOND
01550        PRINT 816, HAFSEC
01560  816   FORMAT(' HAFSEC=',F7,2)
01570        GO TO 9999
01580  17    LVPEP=AVGX/(HAFSEC*2.)
01590 C      LEFT VENTRICULAR PRE EJECTION PERIOD
01600        PRINT 817,LVPEP,N
01610  817   FORMAT(' LVPEP=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01620        GO TO 9999
01630  18    LVET=AVGX/(2.*HAFSEC)
01640 C      LEFT VENTRICULAR EJECTION TIME
01650        PRINT 818,LVET,N
01660  818   FORMAT(' LVET=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01670        GO TO 9999
01680  19    RVPEP=AVGX/(2.*HAFSEC)
01690 C      RIGHT VENTRICULAR PRE EJECTION PERIOD
01700        PRINT 819, RVPEP,N
01710  819   FORMAT(' RVPEP=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS'
01720        GO TO 9999
01730  20    RVET=AVGX/(2.*HAFSEC)
01740 C      RIGHT VENTRICULAR EJECTION TIME
01750        PRINT 820, RVET, N
01760  820   FORMAT(' RVET=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01770        GO TO 9999
01780  21    HR=120.*HAFSEC/AVGX
01790 C      HEART RATE: TAKE LENGTH OF MINUTE AND DIVIDE BY LENGTH O
R
01800        PRINT 821, HR,N
01810  821   FORMAT (' HR=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01820        GO TO 9999
01830  22    MVEF=AVGY/AVGX*2.*HAFSEC
01840 C      MITRAL VALVE EF SLOPE
01850        PRINT 822,MVEF,N
01860  822   FORMAT(' MVEF=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01870        GO TO 9999
01880  23    TVEF=AVGY/AVGX*2.*HAFSEC
01890 C      TRICUSPID VALVE EF SLOPE
01900        PRINT 823, TVEF,N
01910  823   FORMAT(' TVEF=',F7.2,2X,'AVERAGED OVER',I3,2X,'TRIALS')
01920        GO TO 9999
01930  24    PRINT 701
01940  701   FORMAT (' PUT INTO GRAPHICS MODE')
01950        READ 824, AREA
01960 C      THIS IS THE AREA OF THE LV IN 2 DIMENSIONS FROM REAL TIM
01970  824   FORMAT(F9.4)
01980        PRINT 702,AREA
01990  702   FORMAT(' AREA=',F7.2,' RETURN GRAPHICS TO POINT MODE')
02000        AREA=AREA*6.45
```

```
02010        GO TO 700
02020  25    LONGAX=SQRT(AVGX**2.+AVGY**2.)
02030        PRINT 706,LONGAX
02040  706   FORMAT(' LONGAX=',F7.2)
02050 C      THIS IS THE LONG AXIS ACROSS THE AREA SECTION (REAL TI
02060        GO TO 9999
02070  8888  CONTINUE
02080 C      DO COMPUTED VALUES
02090        LVEDV=-19.12+14.58*LVEDD+.62*LVEDD**3.
02100        LVESV=-19.12+14.58*LVESD+.62*LVESD**3.
02110        IF(LVEDD.GE.2.)EF=(LVEDV-LVESV)/LVEDV
02120        IF(LVEDD.LT.2.)EF=-69.
02130        FS=(LVEDD-LVESD)/LVEDD
02140        VCF=FS/LVET
02150        LPEPET=LVPEP/LVET
02160        RPEPET=RVPEP/RVET
02170        LVPEPC=LVPEP+.6*HR
02180        RVPEPC=RVPEP+.5*HR
02190        LVETC=LVET+1.6*HR
02200        RVETC=RVET+1.5*HR
02210        LAAO=LAS/AOS
02220        SPLPWD=SEPD/LVPWD
02230        WSDS=LVPWS/LVESD
02240        LVCAVP=WSDS*225.
02250        SYSGRD=LVCAVP-BP
02260        BP=DIASBP+(SYSBP-DIASBP)/3
02270        PRINT 707
02280  707   FORMAT(' THIS IS THE PRINTOUT'////)
02285        PRINT 161,BSA
02286  161   FORMAT(' THE BSA IS', F5.2)
02290        PRINT 160,BP
02300        PRINT 821,HR
02310        PRINT 801,RVAWD
02320        PRINT 802,RVAWS
02330        PRINT 803,RVDD
02340        PRINT 804,SEPD
02350        PRINT 805,SEPS
02360        PRINT 806,LVESD
02370        PRINT 807,LVEDD
02380        PRINT 808,LVPWD
02390        PRINT 809,LVPWS
02400        PRINT 810,LAS
02410        PRINT 811,AOS
02420        PRINT 812,PA
02430        PRINT 813,MVDE
02440        PRINT 814,TVDE
02450        PRINT 817,LVPEP
02460        PRINT 818,LVET
02470        PRINT 819,RVPEP
02480        PRINT 820,RVET
```

```
02480          PRINT 820,RVET
02490          PRINT 822,MVEF
02500          PRINT 823,TVEF
02510          PRINT 500,LVEDV
02520   500    FORMAT(' LVEDV(MEYER)=',F7.2)
02530          PRINT 501,LVESV
02540   501    FORMAT(' LVESV(MEYER)=',F7.2)
02550          PRINT 502,EF
02560   502    FORMAT(' EF=',F7.2)
02570   160    FORMAT(' MEAN BP=',F6.1)
02580          SV=LVEDV-LVESV
02590          PRINT 550,SV
02600   550    FORMAT(' THE STROKE VOLUME IS',F8.2)
02610          CO=SV*HR
02620          PRINT 551,CO
02630   551    FORMAT(' THE CARDIAC OUTPUT IS',F9.2)
02635          CI=CO/BSA
02636          PRINT 552,CI
02637   552    FORMAT(' THE CARDIAC INDEX IS',F9.2)
02640          PRINT 503,FS
02650   503    FORMAT(' FS=',F7.2)
02660          PRINT 504,VCF
02670   504    FORMAT(' VCF=',F7.2)
02680          PRINT 505,LPEPET
02690   505    FORMAT(' LVPEP/ET=',F7.2)
02700          PRINT 506,RPEPET
02710   506    FORMAT(' RVPEP/ET=',F7.2)
02720          PRINT 515,LVPEPC
02730   515    FORMAT(' LVPEPC=',F7.2)
02740          PRINT 507,RVPEPC
02750   507    FORMAT(' RVPEPC=',F7.2)
02760          PRINT 508,LVETC
02770   508    FORMAT(' LVETC=',F7.2)
02780          PRINT 509,RVETC
02790   509    FORMAT(' RVETC=',F7.2)
02800          PRINT 510,LAAO
02810   510    FORMAT(' LA/AO=',F7.2)
02820          PRINT 511,SPLPWD
02830   511    FORMAT(' SEPTUM/LVPWD=',F7.2)
02840          PRINT 512,WSDS
02850   512    FORMAT (' WS/DS=',F7.2)
02860          PRINT 513,LVCAVP
02870   513    FORMAT(' ESTIMATED LV CAVITY PRESSURE=',F7.2)
02880          PRINT 514,SYSGRD
02890   514    FORMAT(' ESTIMATED SYSTOLIC GRADIENT=',F7.2)
02900 C        VOLUME CALCULATIONS ON REAL TIME
02910          VOL=8.*AREA**2./(3.*3.14*LONGAX)
02920          PRINT 888,VOL
02930   888    FORMAT (' THE LV CAVITY VOLUME BY REAL TIME IS ',F7.2)
02940          STOP
02950          END
```

```
L SUM.FORT
 SUM.FORT
          SUBROUTINE SUM
          COMMON N,LENGTH,XSTAND,YSTAND,AVGX,AVGY,P,X,Y
          INTEGER P
          REAL LENGTH
 C        THIS ROUTINE DEALS WITH AVERAGING LINE SEGMENT VALUES.
 C        IT HAVDLES SEPARATELY Y INPUTS(P=1) , XINPUTS(P=2), AND
 C        AND COMBINED X AND Y INPUTS(P=3).  IT AVERAGES THE
 C        LINE SEGMENTS AND RETURNS THAT NUMBER AND THE NUMBER OF
 C        TRIALS USED IN THE AVERAGE.  TO END THE POINT INPUT,
 C        MERELY SELECT A CONTROL GRID, THE PROGRAM RECOGNIZES THAT
 C        Y IS LESS THAN 4 AND IT RETURNS THE AVERAGED LINE SEGMENT
 C        TO BE EVALUATED INTHEAPPROPRIATE WAY.  IF A MISTAKE IS
 C        MADE, MERELY HIT THE SAME CONTROL GRID AND START AGAIN.
 C        IF YOU HIT A CONTROL GRID, YOU MUST REINPUT THAT DATA,
 C        FOR THE PREVIOUS DATA FOR THAT GRID WILL BE RESET TO ZERO
          AVGY=0.
          AVGX=0.
          SUMX1=0.
          SUMX2=0.
          SUMY1=0.
          SUMY2=0.
          N=0
 C        DIVIDE UP PROGRAM IN TERMS OF P VALUES
          IF(P-2)81,82,83
 C        ENTER FIRST DATA POINT
   81     READ 120,X,Y
          PRINT 120,X,Y
   120    FORMAT(F6.2,F7.2)
 C        SET UP POINT WITH RESPECT TO STANDARD ORIGIN
          X=X-XSTAND
          Y=Y-YSTAND
 C        CHECK IF CONTROL GRID
          IF(Y.LT.4.)GO TO 91
 C        MAKE LENGTH CORRECRTION AND CHANGE TO CMS
          Y1=Y*2.54*LENGTH
          READ 120,X,Y
          PRINT 120,X,Y
          X=X-XSTAND
          Y=Y-YSTAND
          IF(Y.LT.4.)GO TO 91
          Y2=Y*2.54*LENGTH
 C        SET THE COUNTER FOR THE NUMBER OF TRIALS
          N=N+1
 C        ADD THE Y VALUES FOR AVERAGING
          SUMY1=SUMY1+Y1
          SUMY2=SUMY2+Y2
          GO TO 81
   91     IF(N.EQ.0) RETURN
```

```
00490 C      RETURN IF N=0 BECOUSE THIS MEANS A CONTROL GRID WAS SELECT
00500        AVGY=ABS(SUMY2-SUMY1)/N
00510        RETURN
00520 C      THIS IS FOR P=2
00530  82    READ 120,X,Y
00540        PRINT 120,X,Y
00550        X=X-XSTAND
00560        Y=Y-YSTAND
00570        IF(Y.LT.4.)GO TO 92
00580        X1=X*2.54
00590        READ 120,X,Y
00600        PRINT 120,X,Y
00610        X=X-XSTAND
00620        Y=Y-YSTAND
00630        IF(Y.LT.4.) GO TO 92
00640        X2=X*2.54
00650        N=N+1
00660        SUMX1=SUMX1+X1
00670        SUMX2=SUMX2+X2
00680        GO TO 82
00690  92    IF(N.EQ.0) RETURN
00700        AVGX=ABS(SUMX2-SUMX1)/N
00710        RETURN
00720 C       DO THE SAME FOR P=3 (X AND Y CONSIDERED TOGETHER)
00730  83    READ 120,X,Y
00740        PRINT 120,X,Y
00750        X=X-XSTAND
00760        Y=Y-YSTAND
00770        IF(Y.LT.4.) GO TO 93
00780        X1=X*2.54
00790        Y1=Y*2.54*LENGTH
00800        READ 120,X,Y
00810        PRINT 120,X,Y
00820        X=X-XSTAND
00830        Y=Y-YSTAND
00840        IF(Y.LT.4.) GO TO 93
00850        X2=X*2.54
00860        Y2=Y*2.54*LENGTH
00870        N=N+1
00880        SUMX1=SUMX1+X1
00890        SUMX2=SUMX2+X2
00900        SUMY1=SUMY1+Y1
00910        SUMY2=SUMY2+Y2
00920        GO TO 83
00930  93    IF(N.EQ.0) RETURN
00940        AVGX=(SUMX2-SUMX1)/N
00950        AVGY=(SUMY2-SUMY1)/N
00960        RETURN
00970        END
READY
```

```
EDIT
L
00010          SUBROUTINE BLOOD(XSTAND,YSTAND,SYSBP,DIASBP)
00020          INTEGER NEWX(3),BP(2),SYSBP,DIASBP
00060          BP(1)=0
00070          BP(2)=0
00080          PRINT 100
00090    100   FORMAT(' READ IN SYSTOLIC BP')
00100          L=1
00110      7   NEWX(1)=0
00120          NEWX(2)=0
00130          NEWX(3)=0
00131          DO 8 N=1,3
00132          READ 101,X,Y
00133          PRINT 101,X,Y
00140    101   FORMAT(F6.2,F7.2)
00150          NEWY=Y-YSTAND
00160          IF(NEWY.GT.1)N=N-1
00170          IF(NEWY.GT.1)GO TO 17
00180          NEWX(N)=X-XSTAND-1
00190      8   CONTINUE
00200     17   NM1=N-1
00210          NM2=N-2
00220          IF(N-2)3,4,5
00230      3   NM1=3
00240      4   NM2=3
00250      5   BP(L)=NEWX(N)+NEWX(NM1)*10+NEWX(NM2)*100
00260          IF(L.EQ.2)GO TO 19
00270          PRINT 102
00280    102   FORMAT(' READ IN DIASTOLIC BP')
00290          L=2
00300          GO TO 7
00310     19   SYSBP=BP(1)
00320          DIASBP=BP(2)
00330          PRINT 103,SYSBP,DIASBP
00340    103   FORMAT(I4,I4)
00350          RETURN
00360          END
END OF DATA
```

```
READY
L

ENTER DATA SET NAME  -
BODY.FORT

 BODY.FORT
00010          SUBROUTINE BODY(XSTAND,YSTAND,BSA)
00020          INTEGER NUM(3)
00030          NUM(1)=0
00040          NUM(2)=0
00050          NUM(3)=0
00060          PRINT 100
00070    100   FORMAT(' READ IN BODY SURFACE AREA')
00080          DO 28 N=1,3
00100          READ 101,X,Y
00110          PRINT 101,X,Y
00120    101   FORMAT(F6.2,F7.2)
00130          NEWY=Y-YSTAND
00140          NEWX=X-XSTAND
00160          IF(NEWY.GT.1.AND.NEWX.EQ.5)GO TO 17
00170     28   NUM(N)=NEWX-1
00180     17   BSA=NUM(1)+.1*NUM(2)+.01*NUM(3)
00190          PRINT 103,BSA
00200    103   FORMAT(F5.2)
00210          RETURN
00220          END
READY
```

Trial Run

```
EXEC M

INPUT POINTS
+01.51 +02.74

 1.51   2.74
+06.16 +04.13

 6.16   4.13
+04.84 +07.51

 4.84   7.51
+04.83 +07.18

 4.83   7.18
+07.12 +04.23

 7.12   4.23
LENGTH=    1.19
+05.04 +06.98

 5.04   6.98
+06.03 +06.95

 6.03   6.95
+02.11 +05.32

 2.11   5.32
HAFSEC=    2.51
+03.05 +07.02

 3.05   7.02
+04.70 +06.98

 4.70   6.98
+04.80 +06.98

 4.80   6.98
+06.36 +06.95

 6.36   6.95
+06.36 +06.95

 6.36   6.95
+07.60 +06.93

 7.60   6.93
+07.99 +03.15
```

```
 7.01   3.22
LVEDD=   4.15  AVERAGED OVER  3  TRIALS
+07.03 +07.68

 7.03   7.68
+07.24 +06.88

 7.24   6.88
+07.32 +07.63

 7.32   7.63
+07.58 +06.94

 7.58   6.94
+07.69 +07.62

 7.69   7.62
+07.74 +06.92

 7.74   6.92
+08.01 +05.29

 8.01   5.29
LVESD=   2.21  AVERAGED OVER  3  TRIALS
READ IN SYSTOLIC BP
+03.02 +03.12

 3.02   3.12
+04.06 +03.21

 4.06   3.21
+02.07 +03.28

 2.07   3.28
READ IN DIASTOLIC BP
+10.07 +03.12

10.07   3.12
+02.11 +03.33

 2.11   3.33
+10.03 +05.17

10.03   5.17
120  80
+08.99 +05.13
```

```
 8.99   5.13
READ IN BODY SURFACE AREA
+03.12 +03.18

 3.12   3.18
+07.98 +03.14

 7.98   3.14
+01.99 +03.26

 1.99   3.26
1.60
+07.09 +05.16

 7.09   5.16
THIS IS THE PRINTOUT



THE BSA IS 1.60
MEAN BP=  93.0
HR=  80.09  AVERAGED OVER
LVESD=    2.21  AVERAGED OVER
LVEDD=    4.15  AVERAGED OVER
LVEDV(MEYER)=  85.77
LVESV(MEYER)=  19.84
EF=   0.77
THE STROKE VOLUME IS    65.93
THE CARDIAC OUTPUT IS  5280.05
THE CARDIAC INDEX IS  3300.03
READY
```

Appendix B

Protocol for Etomidate Study

SUMMARY

In modern anesthesia, apart from the requirements of freedom from pain, muscle relaxation, and cardiovascular and respiratory stability and control, growing importance is placed on making the experience of anesthesia as comfortable as possible for the patient. Rapid and pleasant induction may be all that matters to the patient. But the safety of the agents used should be the first concern of the anesthesiologists. Although the available induction hypnotics are often far from harmless for the cardiovascular system, most anesthesiologists have obviously highly valued the advantage of rapid onset of sleep.

The pharmacological profile of etomidate, a pure hypnotic of high potency, and short duration with a wide safety margin and minimum effect on the cardiovascular and respiratory systems and which causes no release of histamine and no known organ toxicity or biochemical and hematological changes, suggests that it might be of value for the induction of anesthesia.

I. Background

AIM: To observe the effects of etomidate and thiopental on the cardiovascular system in surgical patients.

PHASE: Efficacy and Safety--Phase III

MEETING WITH FDA: Not applicable.

II. Objectives

To determine whether etomidate offers cardiovascular advantages over thiopental in surgical patients.

III. Investigators

A. Principal Investigator

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B. Co-Investigators

Charles Kleinman, M.D.
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Department of Anesthesiology
Yale University Hospital
School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

C. Clinical Facilities

The clinical facilities and laboratories of the Yale University School of Medicine will be employed in this study.

D. Institutional Review

The Research Committee of Yale University will review and approve this protocol and record form before any work is started.

E. Informed Patient Consent

Written informed patient consent will be obtained from all patients before entering this study.

IV. Experimental Plans

A. Patients

1. Characterization of the study group

The study will consist of 40 patients (male

2. Source of patients

   All surgical patients of the Yale University - New Haven Hospital may participate in this study.

3. Criteria for inclusion or exclusion of patients

   This study will consist of 40 patients (male and/or female) who are candidates for intravenous induction of general anesthesia. All surgical patients described as physical status 1, 2, 3, or 4, definition adopted by the American Society of Anesthesiologists, will be acceptable for this study.

   All patients scheduled for emergency surgery, females of child bearing potential and patients under 16 years of age will be excluded.

4. Concurrent medications

   All concurrent medications will be continued in the peri-operative period as clinically indicated.

B. Procedure

1. Experimental drug

   Etomidate 2 mg in a vehicle consisting of propylene glycol 35% (v/v) in sterile water for injection.

   Batch numbers - not assigned to date.

   Etomidate injectable 2 mg per ml for intravenous administration will be supplied by Janssen R & D, Inc., 501 George Street, New Brunswick, New Jersey 08903

2. Control drug - Thiopental

3. Type of control

   Alternating assignment with control drug

4. Treatment plan (see flow chart, page 8, and schematic page 9)

   a. Following agreement by the attending anesthesiologist, surgeon, and anesthetic evaluation, the patient will be told of the purpose of the study. If he/she agrees to participate, a consent form will be signed.

b. Preoperative cardiovascular evaluation will include routine measurements of blood pressure and pulse.

Approximately 60-90 minutes following premedication, which will be: Morphine sulfate 0.1-0.2 mg/kg and scopolamine .006 mg/kg; another set of hemodynamic measurements will be obtained.

c. Anesthesia will then be induced with either thiopental 4 mg/kg or etomidate 0.3 mg/kg. Alternate patients will be used for each drug (see allocation table, pages 10-12). If in the opinion of the investigator the patient regains consciousness, additional doses of hypnotic may be given. These doses will be one-half the initial dose.

d. Rate and site of the injection will be the same for both of the hypnotics, and will be left to the investigator's discretion. The hypnotics will be administered through an I.V. line in a peripheral vein. The rate and site of the injection will be recorded. An injection over 60 seconds in a large vein is recommended.

e. Following loss of consciousness, the patient will be maintained on nitrous oxide/oxygen 60/40 as is customary. Hemodynamic measurements will be made for three minutes. At 3 minutes, 10 cc's of blood will be drawn for determination of drug levels.

f. Adequate ventilation will be assured by clinical observations and measurement of end-tidal gas samples from the anesthesia circuit.

g. The investigators will also correlate other hemodynamic data obtained from patients who clinically require more extensive monitoring (e.g., arterial catheter, Swan-Ganz catheter). If arterial catheters have been placed, a control and three minute arterial blood gas will be obtained.

h. Further echocardiographic measurements during the perioperative period will be made if warranted.

i. Doctor's standard choice of postoperative antiemetics and/or analgesics, etc., will be employed.

The record form to be used is attached.

5. Clinical observations

a. Entry requirements: See IV A. 2. Source of patients.

b. Critical basic measurements in final analysis:

Measurements

1. Pulse Rate
2. Arterial pressure, systolic and diastolic
3. Heart rate and rhythm
4. Echocardiogram
5. Central Venous Pressure
6. Pulmonary artery Pressure, systolic and diastolic
7. Pulmonary Wedge Pressure
8. Cardiac output (Thermal dilution) where clinically indicated for patient care.

c. Derived hemodynamic profile may include:

1. Cardiac Index
2. Stroke Index
3. Left Ventricular stroke work index
4. Pulmonary Vascular resistance
5. Total peripheral vascular resistance
6. Left Ventricular end diastolic volume
7. Ejection Fraction
8. Velocity of Circumferential fiber shortening
9. Systolic time intervals

6. Metabolic studies

Arterial blood gas values will be determined pre- and posthypnotic. (See Section IV, B, 4g).

7. If any serious adverse effects should occur, the patient will be removed from the study and the condition treated promptly. All side effects must be recorded on the case record form.

If any severe or unusual reactions occur, please immediately call Dr. Jo Brugmans or Mr. Steven Schlossberg at (201) 524-9741 of Janssen R & D, Inc., New Brunswick, New Jersey 08903. If no reply, please call (201) 524-0400, a 24-hour emergency number.

8. Conditions and procedures for removing a patient from the study

Any severe or life-threatening event will be sufficient to remove a patient from the study

9. Conditions for terminating or extending the entire study

The entire study may be terminated if an unusual number of adverse reactions occur by notifying the sponsor. The study may be extended if deemed necessary by the investigator only with the mutual consent of the sponsor.

10. Analysis of data

At completion of the study, it is expected that data will be available on the following points in particular: Hemodynamic cardiovascular measurements and calculations for both hypnotics both prior to administration and up to three minutes after the administration of the hypnotics.

11. Radioactivity specifications - Not applicable.

V. Monitoring and Data Processing

A. Monitors - Janssen R & D, Inc., New Brunswick, New Jersey 08903

J. Wm. D. Cornett, M.D. Med. Res. Consultant	Steven Schlossberg Project Monitor
Jo Brugmans, M.D. Vice Pres, and Gen. Mgr.	Clinical Research Assistant
Roger L. Aspeling Director of Clin. Res.	

B. Statistician

Mr. J. Dony

C. Execution

1. Estimated timetable

The duration of the study is estimated at not more than four months.

2. Checks and controls of clinical data collection

All forms will be checked by the principal monitor and statistician. Any possible inaccuracy on the anesthesiologist's form will be checked with the investigator.

3. Data processing procedures

All data from the record forms will be first transcribed to computer input records, then punched and repunched for control. All pertinent and relevant data will be finally summarized in tables.

4. .Data processing checks and controls

Not applicable

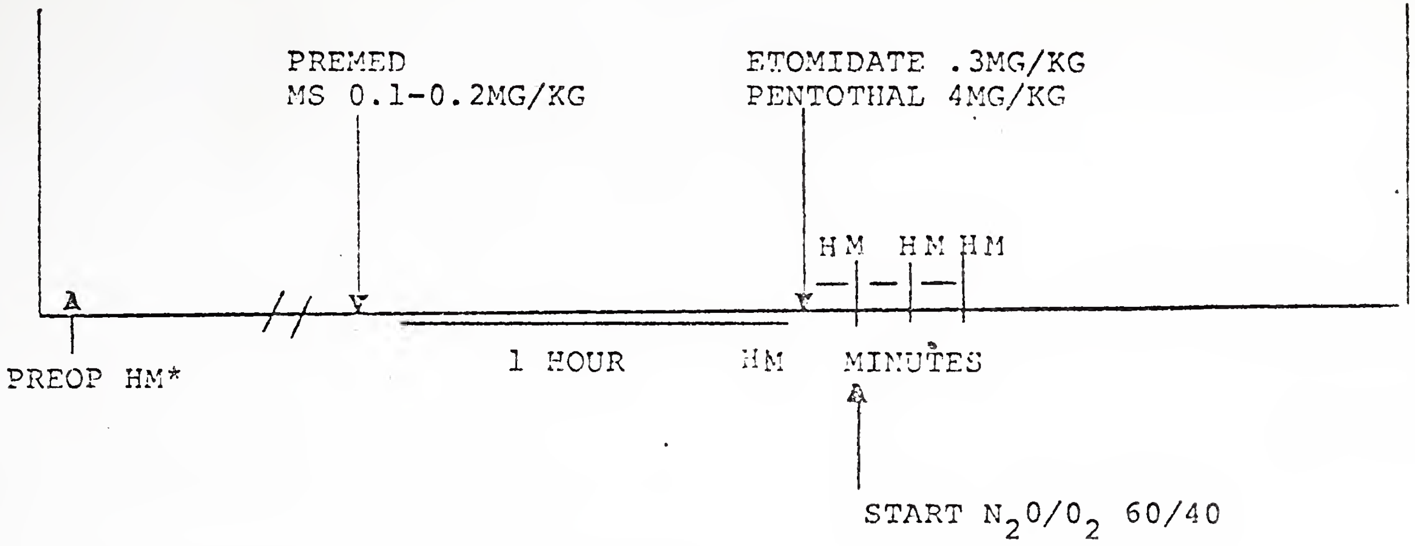
5. Incidence of transcribing errors

Transcribing errors will be kept to a minimum since all record forms will be transcribed by a well-trained and qualified statistician. A random test will be done by the principal statistician in order to check transcribing accuracy.

Missing values in the data will be kept to a minimum as the studies will be conducted by well-qualified investigators and properly monitored by well-trained Clinical Research Associates.

	ETOMIDATE STUDY FLOW CHART
BEFORE HYPNOTIC	1. Select patient who meets acceptance criteria. 2. Administer premedication according to protocol. 3. Hemodynamic measurements immediately prior to hypnotic.
DURING HYPNOTIC	4. Administer hypnotic as shown in allocation chart.
AFTER HYPNOTIC	5. At one minute intervals up to 3 minutes after administration of hypnotics, perform hemodynamic measurements and record results. 6. Continue with further induction (intubation, muscle relaxants, analgesics, etc.)

SCHEMA FOR STUDY



*HM = HEMODYNAMIC MEASUREMENTS

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